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formed upon dissolution. In ideal solutions, for example, $n = 1$ for glucose, $n = 2$ for sodium chloride or magnesium sulfate, $n = 3$ for calcium chloride, and $n = 4$ for sodium citrate.

The ideal osmolar concentration may be determined according to the formula:

$$\text{osmolar concentration (mOsmol / liter)} = \text{mOsM} =$$

$$= \frac{\text{wt. of substance (g/liter)}}{\text{mol. wt. (g)}} \times \text{number of species} \times 1000.$$

As the concentration of the solute increases, interaction among solute particles increases, and actual osmolar values decrease when compared to ideal values. Deviation from ideal conditions is usually slight in solutions within the physiologic range and for more dilute solutions, but for highly concentrated solutions the actual osmolarities may be appreciably lower than ideal values. For example, the ideal osmolarity of 0.9% Sodium Chloride Injection is 9/58.4 × 2 × 1000 = 308 milliosmoles per liter. In fact, however, n is slightly less than 2 for solutions of sodium chloride at this concentration, and the actual measured osmolarity of 0.9% Sodium Chloride Injection is about 286 milliosmoles per liter.

The theoretical osmolarity of a complex mixture, such as Protein Hydrolysate Injection, cannot be readily calculated. In such instances, actual values of osmolar concentration are to be used to meet the labeling requirement set forth in the individual monograph. They are determined by calculating the osmolarity from measured values of osmolal concentration and water content. Each osmole of solute added to 1 kg of water lowers the freezing point approximately 1.86° and lowers the vapor pressure approximately 0.3 mm of mercury (at 25°). These physical changes are measurable, and they permit accurate estimations of osmolal concentrations.

Where osmometers that measure the freezing-point depression are employed, a measured volume of solution (usually 2 mL) is placed in a glass tube immersed in a temperature-controlled bath. A thermistor and a vibrator are lowered into the mixture, and the temperature of the bath is decreased until the mixture is super-cooled. The vibrator is activated to induce crystallization of the water in the test solution, and the released heat of fusion raises the temperature of the mixture to its freezing point. By means of a Wheatstone bridge, the recorded freezing point is converted to a measurement in terms of milliosmolality, or its near equivalent for dilute solutions, milliosmolarity. The instrument is calibrated by using two standard solutions of sodium chloride that span the expected range of osmolarities.

Osmometers that measure the vapor pressures of solutions are less frequently employed. They require a smaller volume of specimen (generally about 5 µL), but the accuracy and precision of the resulting osmolality determination are comparable to those obtained by the use of osmometers that depend upon the observed freezing points of solutions.

Labeling—Where an osmolarity declaration is required in the individual monograph, the label states the total osmolar concentration in milliosmoles per liter. Where the contents are less than 100 mL, or where the label states that the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in milliosmoles per milliliter.

⟨786⟩ PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

Sieving is one of the oldest methods of classifying powders by particle size distribution. Sieving is most suitable where the majority of the particles are larger than about 75 µm, although it can be used for some powders having smaller particle sizes where the method can be validated. In pharmaceutical terms, sieving is usually the method of choice for classification of the coarser grades of single powders. It is a particularly attractive method in that powders are classified only on the basis of particle size, and in most cases the analysis can be carried out in the dry state.

Among the limitations of the sieving method are the need for an appreciable amount of sample (normally at least 25 g) and difficulty in sieving oily or other cohesive powders that tend to clog the sieve openings. The method is essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length.

This method is intended for estimation of the total particle size distribution of a single material. It is not intended for determination of the proportion of particles passing or retained on one or two sieves.

Estimate the particle size distribution as described under *Method I*, unless otherwise specified in the individual monograph. *Method I* is the dry sieving method. Where difficulty is experienced in reaching the endpoint (i.e., material does not readily pass through the sieves) or when it is necessary to use the finer end of the sieving range (below 75 µm), *Method II*, which is a wet sieving technique, may be used; however, in the latter case serious consideration should be given to the use of an alternative particle-sizing method.

Principles of Analytical Sieving—Analytical test sieves are constructed from a woven-wire mesh, which is of simple weave that is assumed to give nearly square apertures and is sealed into the base of an open cylindrical container. The basic analytical method involves stacking the sieves on top of one another in ascending degrees of coarseness, and then placing the test powder on the top sieve.

The nest of sieves is subjected to a standardized period of agitation, and then the weight of material retained on each sieve is accurately determined. The test gives the weight percentage of powder in each sieve size range.

This sieving process for estimating the particle size distribution of a single pharmaceutical powder is generally intended for use where at least 80% of the particles are larger than 75 µm. The size parameter involved in determining particle size distribution by analytical sieving is the *length of the side of the minimum square aperture through which the particle will pass.*

TEST SIEVES

Test sieves suitable for pharmacopeial tests conform to the most current edition of American Society for Testing and Materials (ASTM) Specification E 11 U.S. Standard Sieve Series (see *Table 1*). Unless otherwise specified in the monograph, use those ASTM sieves listed in *Table 1* as recommended USP sieves.

Table 1. Sizes of Standard Sieve Series in Range of Interest.

Sieve Size	Sieve U.S. No.	ASTM E 11*	Recommended USP Sieves
4.00 mm	5	X	X
3.35 mm	6	X	
2.80 mm	7	X	X
2.36 mm	8	X	
2.00 mm	10	X	X
1.70 mm	12	X	
1.40 mm	14	X	X
1.18 mm	16	X	
1.00 mm	18	X	X
850 µm	20	X	
710 µm	25	X	X
600 µm	30	X	
500 µm	35	X	X
425 µm	40	X	
355 µm	45	X	X
300 µm	50	X	
250 µm	60	X	X
212 µm	70	X	
180 µm	80	X	X
150 µm	100	X	
125 µm	120	X	X
106 µm	140	X	
90 µm	170	X	X
75 µm	200	X	
63 µm	230	X	X
53 µm	270	X	